The formation of methyl iodide in the reaction mixture can be accounted for by

$$CH_3OH + HI = CH_3I + H_2O \qquad (4)$$

which may be one of the steps in the mechanism of (3). The net change in the reaction mixture from the time of mixing is given by a combination of the equations (2), (3), (4). When the reaction is carried to completion the contribution from (4) is zero and the net effect is the combination of (2) and (3) so as to give (1).

No mechanisms which we have devised for the reactions (2) and (3) will account for all the experimental observations. The possibility that methane is formed from methyl iodide and hydrogen iodide was considered. Assuming that the iodine not in the form of hydrogen iodide or free iodine was all methyl iodide, we calculated the rate of formation of methane from Ogg's data. The observed rate during the steady state was 12.6×10^{-7} mole/cc./hr. and the calculated rate was 18.5×10^{-7} mole/cc./hr. The agreement is not sufficiently good to warrant the conclusion that the methane must be formed by this reaction but it seems to be a reasonable possibility at these temperatures. The constancy of the rate of formation of methane during a large percentage of the reaction could be accounted for by this reaction since the concentrations of methyl iodide and hydrogen iodide are constant over the same range.

Summary

The iodine sensitized decomposition of methyl alcohol has been studied at 325°. It has been shown that although the net effect in systems in which the reaction was carried to completion may be represented by the equation $3CH_3OH = 2CH_4 + CO + 2H_2O$ this is the resultant of two other reactions. One of these is the oxidation of the alcohol to carbon monoxide by the iodine, the other the reduction of the alcohol to methane by hydrogen iodide.

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The Dilituric (5-Nitrobarbituric) Acid of Some Physiologically Important Bases

BY C. E. REDEMANN AND CARL NIEMANN

The qualitative or quantitative isolation of basic compounds from natural sources is, in general, most satisfactorily accomplished when the base in question can be obtained as the salt of a suitable acid.[1] Of the acidic reagents that have been employed in the past, it is certain that compounds such as picric acid, styphnic acid, picrolonic acid, nitranilic acid[2] and 3-nitrodiketohydrindene[3] have found the greatest application and it is noteworthy that all of these compounds are characterized by the presence of a contiguous nitrophenolic (or enolic) array in an ensemble of atoms capable of forming a resonating system.

We have found that dilituric acid (5-nitrobarbituric acid) surpasses the above nitro-enolic compounds as a reagent for the isolation of many naturally occurring bases and it is the purpose of this communication to call attention to the properties of some of the salts of this acid and their use in isolation problems.

Dilituric acid[4] prepared by the direct nitration of barbituric acid[4b,c,f,h,i] is readily purified. The solubility of the acid, in millimoles per liter of solution at 25°, in methanol is 99; in 95% ethanol, 85; in water, 63; in absolute ethanol, 35; in acetone, 25; in ethyl ether, 0.9; and in benzene, 0.4. Dilituric acid behaves like a strong monobasic acid and from the electrometric titration of a 0.00904 N aqueous solution it appears that the acid strength of dilituric acid is intermediate between that of picric acid and hydrochloric acid.[5]

Examination of Table I reveals that dilituric acid is a satisfactory reagent for the separation of potassium from binary mixtures containing so-

(1) (a) M. Bergmann and C. Niemann, *J. Biol. Chem.*, **122**, 577 (1937); (b) W. H. Stein, C. Niemann and M. Bergmann, THIS JOURNAL, **60**, 1703 (1938); (c) M. Bergmann and W. H. Stein, *J. Biol. Chem.*, **128**, 217; **129**, 609 (1939); (d) H. R. Ing and M. Bergmann, *ibid.*, **129**, 603 (1939).

(2) B. W. Town, *Biochem. J.*, **30**, 1833 (1936).

(3) (a) G. Wanag, *Ber.*, **69**, 1066 (1936); (b) G. Wanag and A. Lode, *ibid.*, **70**, 547 (1937).

(4) (a) A. Schlieper, *Ann.*, **56**, 23 (1845); (b) A. Baeyer, *ibid.*, **127**, 209 (1863); **130**, 140 (1864); (c) M. Grimaux, *Ann. chim.*, (5) **17**, 278 (1879); (d) M. Ceresole, *Ber.*, **16**, 1134 (1883); (e) R. Bartling, *Ann.*, **339**, 39 (1905); (f) A. F. Holleman, *Rec. trav. chim.*, **16**, 168 (1897); (g) H. Biltz and K. Sedlatscheck, *Ber.*, **57**, 339 (1924); (h) *Org. Syntheses*, **12**, 58 (1932); (i) H. Fredholm, *Z. anal. Chem.*, **104**, 400 (1936).

(5) P. A. Trübsach, *Z. physik. Chem.*, **16**, 718 (1895).

dium,[4i,6] and is an excellent reagent for the isolation of magnesium.[7]

TABLE I

INORGANIC SALTS OF DILITURIC ACID

Diliturate Metal	Mol. wt.	Solubility[a] Mmoles/l.	Appearance
Mg	476.5	0.1	Plates
Ba	517.5	1.3	Powder
Sr	442.7	1.7	Platelets
Cu	461.7	1.8	Needles
K	211.1	3.9	Prisms
Ca	402.2	5.7	Needles
Ag	352.0	12	Platelets
Na	195.0	38	Needles or prisms

[a] In water at 25°.

TABLE II

ORGANIC SALTS OF DILITURIC ACID

Diliturate Amine	Mol. wt.	Solubility[a] Mmoles/l.	Appearance
Simple Amines			
Ethylenediamine	406.2	0.6	Powder
Ammonia	190.1	7.3	Flakes
Ethylamine	218.1	13	Needles
Dimethylamine	218.1	15	Powder
Phenylisopropylamine	326.2	15	Needles
n-Butylamine	246.1	17	Scales
n-Amylamine	260.2	24	Scales
Aniline	266.1	26	Plates
Methylamine	204.1	37	Powder
Tri-*n*-butylamine	358.3	51	Prisms
Simple Heterocyclic Bases			
Quinoline	302.1	23	Needles
Imidazole	242.1	36	Prisms
Pyridine	252.1	54	Needles
d(+)Glucobenzimidazole	441.3	65	Needles
Morpholine	260.1	80	Platelets
Alkanolamines			
dl-Ephedrine	338.2	8.7	Platelets
β-Hydroxyphenyl ethylamine	319.2	13	Flat spears
l-Ephedrine	338.2	30	Platelets
d-Pseudoephedrine	365.2	32	Leaves
l-Epinephrine	374.2	37	Flakes
Ethanolamine	234.1	53	Plates
d-Glucosamine	387.2	85	Needles
Triethanolamine	322.2	132	Prisms
1-Amino-2-hydroxypropane	248.1	134	Flakes
Alkaloids			
Quinine	697.3	1.6	Plates
Brucine	812.4	3.7	Plates
Strychnine	734.4	3.9	Needles
Cinchonine	658.3	9.0	Needles
Nicotine	508.2	12.3	Needles
Caffeine	385.2	68	Plates
Amino Acids			
l-Diiodotyrosine	606.0	2.2	Powder
dl-Lysine	492.2	6.4	Scales
l-Histidine	501.2	7.9	Needles
l-Lysine	492.2	9.0	Powder
l-Tyrosine	372.2	10.0	Needles
l-Arginine	347.2	10.2	Needles
l-Cystine	586.3	15	Needles
dl-Phenylalanine	356.2	16	Scales
dl-α-Aminoisobutyric acid	276.1	20	Needles
l-Tryptophan	337.2	20	Needles
dl-α-Aminophenylacetic acid	324.1	28	Prisms
Sarcosine	262.1	34	Needles
Betaine	290.1	34	Needles
dl-α-Amino-*n*-butyric acid	294.2	40	Plates
l-Alanine	281.1	43	Needles
Glycine	248.1	49	Plates
dl-Alanine	281.1	50	Needles
dl-Aspartic acid	306.1	61	Powder
l-Glutamic acid	320.1	67	Powder
dl-γ-Amino-*n*-butyric acid	276.1	77	Scales
dl-Glutamic acid	320.1	90	Needles
l-Cysteine	303.2	92	Needles
l-Aspartic acid	306.1	94	Needles
dl-Leucine	304.2	94	Scales
l-Proline	288.1	100	Scales
l-Asparagine	305.1	103	Powder
l-Leucine	322.2	105	Needles
dl-Valine	290.1	107	Needles
dl-Isoleucine	304.2	107	Needles
dl-Norleucine	304.2	109	Plates
dl-Norvaline	290.1	110	Rosets
dl-Methionine	331.2	112	Plates
dl-Serine	278.1	112	Plates
l-Hydroxyproline	304.1	141	Scales
Proteinogenic Amines			
Guanidine	232.1	7.0	Needles
Tyramine	310.2	8.7	Plates
Histamine	284.1	17	Needles
Phenylethylamine	303.2	19	Needles
Creatinine	286.1	23	Powder
Urea	233.1	36	Powder

[a] In water at 25°.

In Table II we have tabulated the properties of salts formed by the interaction of diluturic acid with seventy-one organic bases. The dilturates of the primary aliphatic amines are surprisingly insoluble in water at 25° and, within limits, the solubility in water increases with increasing chain length. The transition from a primary amine to a secondary amine diliturate is accompanied by a decrease in solubility; however, the salts of the tertiary amines are much more soluble than those of the corresponding secondary amines. The heterocyclic bases, quinoline, imidazole, and pyridine form sparingly soluble dilturates but in con-

(6) (a) H. Frediani, Meeting of the American Chemical Society, Boston, September, 1939; (b) O. C. Dermer and V. H. Dermer, THIS JOURNAL, 61, 3302 (1939).

(7) With the aid of diluturic acid we have been able to establish the presence of magnesium in the crude phospholipids obtained from bovine spinal cord.

trast to morpholine it was found that ethylmorpholine dilituratе was very soluble in water.

The isolation of ethanolamine from the hydrolyzates of phospholipids by the methods hitherto available has been a very laborious task and, still more serious, the methods are not capable of being developed to the point of yielding quantitative data.[8] The observation that ethanolamine dilituratе possesses but limited solubility in water has not only offered a means for the qualitative isolation of this base but in addition has provided a reagent that can be used for the quantitative estimation of ethanolamine and other alkanolamines by the so-called solubility product method of analysis.[1,9] Dilituric acid is also a suitable reagent for the isolation and estimation of glucosamine.

An extensive study of the dilituratеs of the amino acids has been made and in Table II are listed the properties of thirty-four salts. The dilituratеs of the aliphatic monoamino monocarboxylic acids present an interesting situation in that as the length of the side chain increases from zero to three carbon atoms the solubility of the dilituratе increases in a regular manner. Exactly the opposite is observed when one considers the solubility of the amino acids themselves. In addition it was noted that a branching of the side chain resulted in a decrease in the solubility of the dilituratе. Examination of Table II can leave no doubt that there are many amino acid mixtures that can be separated with the aid of dilituric acid. The dilituratеs of the proteinogenic amines are only slightly soluble in water at 25° and it is clear that dilituric acid is a suitable reagent for their isolation.

The fact that dilituric acid is not exceedingly soluble in water at 25° creates a demand for a more soluble form of this reagent. Fortunately the trimethylamine and the ethylmorpholine dilituratеs are very soluble in water and these salts may be used in lieu of the acid.

One of the advantages of isolating bases in the form of their salts is that the base can be easily regenerated. We have found that the regeneration of bases from their dilituratеs can be achieved in the majority of cases by simply replacing the base in question by either ethylenediamine, magnesium or ammonium, as the salts of these three substances are exceedingly insoluble in water. Thus in a typical case, the decomposition of glycine dilituratе with ammonia gave an 89% yield of crystalline glycine.

In conclusion it can be stated that dilituric acid possesses many of the characteristics of the ideal acidic precipitant in that: (a) it is readily available at low cost; (b) in aqueous solution it behaves as a strong monobasic acid thereby diminishing the possibility of forming mixed salts; (c) it is moderately soluble in water and the alcohols; (d) several very soluble salts are known; (e) all of the dilituratеs that were prepared were well-defined crystalline substances thereby facilitating their isolation; (f) the salts were characterized by a wide variation in solubility, thereby permitting fractionation of mixtures; (g) both the acid and the salts possess a high temperature coefficient of solubility which allows ready purification by recrystallization and enhances the possibility of resolving mixtures whose dilituratеs have similar solubilities at any one temperature; and (h) in the majority of cases the base can be obtained easily from the salt by a simple double decomposition.

Experimental

Dilituric Acid (5-Nitrobarbituric Acid).—The acid was prepared according to the directions given in Organic Syntheses.[4h] A solution of 0.2317 g. of thrice recrystallized anhydrous dilituric acid in 150 ml. of water (pH 2.03) was titrated electrometrically and examination of the titration curve revealed that the strength of this acid was intermediate between that of picric acid and hydrochloric acid.

Preparation of the Dilituratеs.—A solution of 5 millimoles of dilituric acid and 5 millimoles of the base[10] (2.5 millimoles for a diacidic base) was prepared with the minimum amount of boiling water and allowed to cool to 25°. The salts were recrystallized one or more times before determining their composition and solubility.

Analysis of the Dilituratеs.—Fifteen to twenty mg. samples of the inorganic salts, dried at 80°, were ignited in the presence of sulfuric acid and the average deviation of the percentage metal found from that calculated was ±0.11. In order to obtain satisfactory values for the carbon and hydrogen content of the organic dilituratеs it was necessary to replace the ordinary Pregl copper oxide–lead chromate combustion zone filling[11] by copper oxide and all of the silver plugs, in front of the combustion zone, by 10% platinized asbestos. In addition the sample, (20–30 mg.) dried at 80°, was mixed with powdered cupric

(8) (a) H. Thierfelder and E. Klenk, "Die Chemie der Cerebroside und Phosphatide," J. Springer, Berlin, 1930; (b) E. Chargaff, *J. Biol. Chem.*, **118**, 417 (1937).

(9) Unpublished observations of the authors taken from a study on the nature of the water soluble bases present in mammalian phospholipids.

(10) We wish to thank Dr. G. Alles for supplying a number of the alkanol- and proteinogenic amines.

(11) F. Pregl, "Die quantitative organische Mikroanalyse," 3rd ed., J. Springer, Berlin, 1930.

oxide prior to ignition. The average deviation of the percentages found from those calculated was ±0.15; the maximum in any case did not exceed 0.3 except for the following salts: ethylamine, % H, calcd. 4.6, found 4.2; *m*-amylamine, % H, calcd. 6.2, found 5.8; *l*-aspartic acid, % H, calcd. 3.3, found 3.7; *dl*-leucine, % C, calcd. 39.4, found 38.9; guanidine, % H, calcd. 3.5, found 3.1.

Determination of Solubilities.—The saturated solutions were approached from the supersaturated side by placing samples saturated at 40–50° and containing an excess of the solid phase in a thermostat at 25.0 ± 0.5° and allowing forty-eight or more hours, with shaking, for the attainment of equilibrium.[12] 10.00-ml. aliquots were withdrawn, evaporated to dryness at 80° and the residues weighed. The solubilities of the various dilituratates, in water at 25°, are given in Tables I and II and those of dilituric acid, in a number of different solvents at 25°, in the text. The over-all accuracy (*i. e.*, reproducibility) of the solubility data in these tabulations is ±4%.

Recovery of Glycine from its Dilituratate.—To 8.4 g. of glycine dilituratate in 100 ml. of hot water was added 3 ml. of 15 *N* ammonium hydroxide. The solution was cooled to room temperature, the precipitate removed and the filtrate evaporated to 20 ml. Upon adding 100 ml. of ethanol to the concentrate, glycine began to precipitate. After cooling to 5° the pure white product was recovered and dried *in vacuo*. The weight was 2.30 g. or 89% of the theoretical amount.

(12) Preliminary experiments with a monovalent salt, soluble in water at 25° to the extent of 50 millimoles per liter, gave identical results, within the limits of experimental error (±2%), when the saturated solution was approached from both sides.

Summary

A number of salts of dilituric acid (5-nitrobarbituric acid) have been prepared and a study of their properties has shown that dilituric acid is a satisfactory reagent for the isolation and determination of many organic and inorganic bases.

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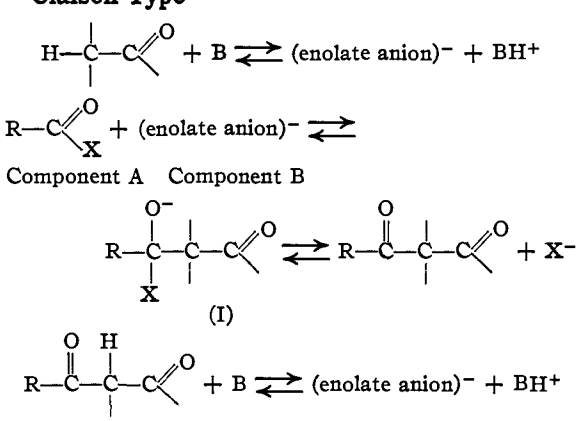
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

Condensations Brought about by Bases. IX. The Relationship between the Claisen and Perkin Types of Condensations[1,2]

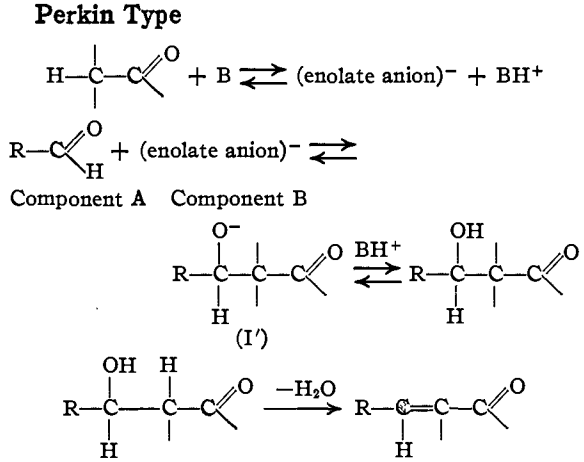
BY CHARLES R. HAUSER AND DAVID S. BRESLOW

The mechanisms for the Claisen[3] (acetoacetic ester) and Perkin[4] types of condensations in the presence of a base B have been represented by the following ionic equations.

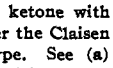
Claisen Type



Perkin Type



The purpose of this paper is to compare these two types of condensation and to discuss certain experiments in which it is possible for either or both types to occur.

It is evident from the above equations that in both the Claisen and Perkin reactions component B is the enolate anion of a compound of the type  (ester, anhydride, aldehyde, ketone, etc.). Component A, however, is different in the two condensations. In the Claisen reaction

(1) Paper VIII, THIS JOURNAL, **62**, 62 (1940).

(2) This paper was presented before the Division of Organic Chemistry at the Baltimore meeting of the American Chemical Society, April, 1939.

(3) Two types of reaction are known as Claisen condensations, the acetoacetic ester type and the condensation of a ketone with benzaldehyde by means of alkali. In the present paper the Claisen condensation refers only to the acetoacetic ester type. See (a) Hauser and Renfrow, THIS JOURNAL, **59**, 1823 (1937); (b) Hauser, *ibid.*, **60**, 1957 (1938).

(4) See Hauser and Breslow, *ibid.*, **61**, 793 (1939).